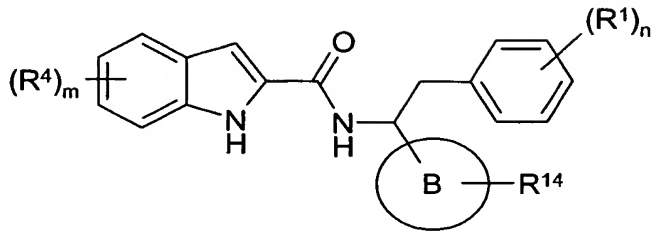
Claims

1. A compound of formula (1):



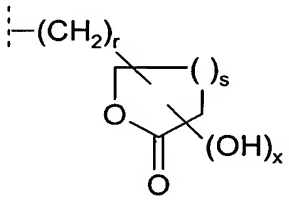
(1)

wherein:

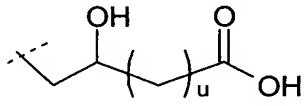
n is 0, 1, or 2;

m is 0, 1, or 2;

R^1 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N*,*N*-(C_{1-4}alkyl)$_2$amino, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, and groups of the formula A or A':



(A)



(A')

wherein x is 0 or 1, r is 0, 1, 2, or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^4 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, and C_{1-4}alkanoyl;

B is phenyl or heterocyclyl;

R^{14} is selected from hydrogen, halo, C_{1-4}alkyl (optionally substituted with 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), C_{1-4}alkoxy, cyano, cyano(C_{1-4})alkyl, -COR^3, (R^2)(R^3)NCO-, and (R^2)(R^3)NSO_2-;

R^2 and R^3 are independently selected from C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl,
1,1-dioxotetrahydrothiopyranyl, fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl (optionally substituted with 1 or 2 R^8 groups), –OR^8, and R^8;

R^8 is independently selected from hydrogen, 2,2-dimethyl-1,3-dioxolan-4-yl, heterocyclyl (optionally substituted on ring carbon or ring nitrogen with 1 or 2 groups selected from hydrogen, nitro, halo, cyano, hydroxy, and C_{1-4}alkyl), (heterocyclyl)C_{1-4}alkyl (wherein the heterocyclyl is optionally substituted on ring carbon or ring nitrogen with 1 or 2 groups selected from hydrogen, nitro, halo, cyano, hydroxy, and C_{1-4}alkyl), aryl (optionally substituted with 1 or 2 groups selected from nitro, halo, cyano, hydroxy, and C_{1-4}alkyl), C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen with 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), -N(OH)CHO, -$CH_2CH(CO_2R^9)N(R^9R^{10})$, -$CH_2OR^9$, ($R^9$)($R^{10}$)N-, –$COOR^9$, -$CH_2COOR^9$, –$CH_2CONR^9R^{10}$, and –$(CH_2)_uCH(NR^9R^{10})CO_2R^9$ (wherein u is 1, 2, or 3);

R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted with 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, 2,2-dimethyl-1,3-dioxolan-4-yl, aryl (optionally substituted with 1 or 2 substituents selected from hydrogen, nitro, halo, hydroxy, and C_{1-4}alkyl), and C_{1-4}alkyl substituted with R^{13}; or R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring is optionally substituted on carbon with 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-(C_{1-4}alkyl)$_2$amino, carbonyl, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_f$(C_{1-4})alkyl (wherein f is 0, 1, or 2), -N(OH)CHO, (R^{11})(R^{12})NCO-, (R^{11})(R^{12})NSO_2-, -$COCH_2OR^{11}$, and (R^{11})(R^{12})N-;

R^{13} is selected from hydroxy, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_d$ (wherein d is 0, 1, or 2), -N(OH)CHO, -C(O)N(R^{11})(R^{12}), (R^{11})(R^{12})NSO_2-, -$COCH_2OR^{11}$, and (R^{11})(R^{12})N-; and

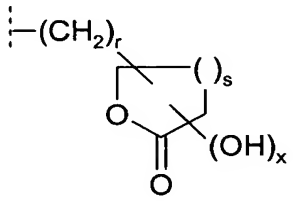
R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, and C_{1-4}alkylS(O)$_e$ (wherein e is 0, 1, or 2);

or a pharmaceutically acceptable salt or prodrug thereof.

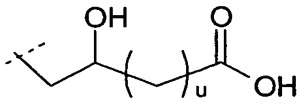
2. A compound of claim 1, wherein

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, cyano, nitro, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, and groups of the formula A or A':



(A')



(A")

wherein x is 0 or 1, r is 0, 1, 2, or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

B is heterocyclyl;

R^{14} is selected from is selected from hydrogen, C_{1-4}alkyl (optionally substituted with 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, -COR^3, (R^2)(R^3)NCO-, and (R^2)(R^3)NSO_2-;

R^2 and R^3 are independently selected from C_{1-4}alkyl (substituted with 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl (substituted with R^8), –OR^8, and R^8;

R^8 is independently selected from hydrogen, furyl (optionally substituted on carbon with 1 or 2 nitro groups), thienyl (optionally substituted on carbon with 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon with 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon with 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, morpholino, pyridyl, phenyl (optionally

substituted with 1 or 2 groups selected from nitro, halo, cyano, hydroxy, and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen with 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl, and aryl(C_{1-4})alkyl), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1, or 2), $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, and $-CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted with 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted with 1 or 2 groups selected from nitro, halo, hydroxy, and cyano), and C_{1-4}alkyl substituted with R^{13}; or

R^9 and R^{10} together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon with 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-$(C_{1-4})_2$alkylamino, carbonyl, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, and C_{1-4}alkyl$S(O)_f$(C_{1-4})alkyl (wherein f is 0, 1, or 2);

R^{13} is selected from C_{1-4}alkoxy, furyl (optionally substituted on carbon with 1 or 2 nitro groups), thienyl (optionally substituted on carbon with 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon with 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon with 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted with 1 or 2 groups selected from nitro, halo, cyano, hydroxy, and C_{1-4}alkyl), pyrazinyl, piperazinyl, and C_{1-4}alkyl$S(O)_d$(C_{1-4})alkyl (wherein d is 0, 1, or 2);

m is 1 or 2; and

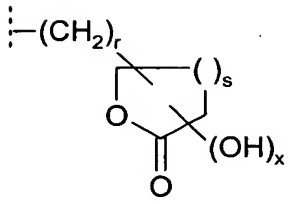
R^4 is hydrogen or halo;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

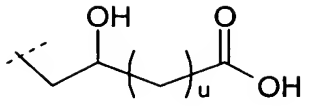
3. A compound of claim 1, wherein:

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl, and groups of the formula A or A'



(A')



(A")

wherein x is 0 or 1, r is 0, 1, 2, or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

B is heterocyclyl;

R^{14} is selected from hydrogen, halo, cyano, C_{1-4}alkoxy, C_{1-4}alkyl (optionally substituted with 1 or 2 hydroxy groups, provided that when there are 2 hydroxy groups they are not substituents on the same carbon), and cyanoC_{1-4}alkyl;

m is 1; and

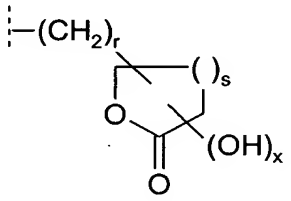
R^4 is chloro;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

4. A compound of claim 1 wherein:

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl, or R^1 is of the formula A or A':



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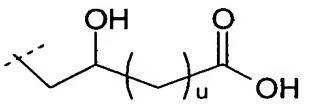


(A")

wherein x is 0 or 1, r is 0, 1, 2, or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

B is phenyl;

R^{14} is selected from C_{1-4}alkyl, cyano(C_{1-4})alkyl, -COR^3, (R^2)(R^3)NCO-, and (R^2)(R^3)NSO_2-;

R^2 and R^3 are independently selected from C_{1-4}alkyl, C_{1-4}alkyl (substituted with R^8), –OR^8, and R^8;

R^8 is independently selected from hydrogen, heterocyclyl (optionally substituted on carbon or nitrogen with 1 or 2 groups selected from nitro, halo, hydroxy, cyano, and C_{1-4}alkyl), (heterocyclyl)(C_{1-4})alkyl (optionally substituted on carbon or nitrogen with 1 or 2 groups selected from nitro, halo, hydroxy, cyano, and C_{1-4}alkyl), aryl (optionally substituted with 1 or 2 groups selected from nitro, halo, cyano, hydroxy, and C_{1-4}alkyl), C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen with 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl, and aryl(C_{1-4})alkyl), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1, or 2), -$(CH_2)_u$CH(CO_2R^9)N(R^9R^{10}) (wherein u is 0, 1, or 2), -CH_2OR^9, (R^9)(R^{10})N-, –$COOR^9$,–CH_2COOR^9, –$CH_2CONR^9R^{10}$, and -$CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted with1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, and phenyl (optionally substituted with 1 or 2 groups selected from nitro, halo, hydroxy, and cyano);

m is 1;

R^4 is chloro;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

5. A compound of claim 1 which is:

methyl (*S*)-5-{1-[(5-chloro-1*H*-indol-2-ylcarbonyl)amino]-2-phenylethyl}oxazole-4-carboxylate;

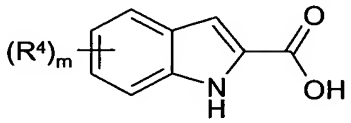
or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

6. A pharmaceutical composition which comprises a compound of claim 1, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof in association with a pharmaceutically acceptable diluent or carrier.

7. A method for the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, comprising administering a compound of claim 1, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

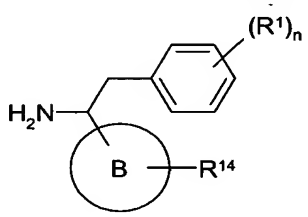
8. A method for the treatment of type 2 diabetes in a warm-blooded animal, comprising administering a compound of claim 1, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

9. A process for the preparation of claim 1, which process comprises:
reacting an acid of the formula (2)



(2)

or an activated derivative thereof; with an amine of formula (3)



(3)

and thereafter if necessary
i) converting a compound of the formula (1) into another compound of the formula (1);
ii) removing any protecting groups; or
iii) forming a pharmaceutically acceptable salt or in-vivo hydrolysable ester.